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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/357,709	07/20/99	BANDER	N 242/026

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EXAMINER	
HUNT, J	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 09/13/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/357,709	Bander
Examiner	**Group Art Unit**
Jennifer Nichols, Nee Hunt	1642

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *24-42* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *24-42* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4,5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Aknowledgement is made of applicant's cancellation of claims 1-23 and 43-67. Claims 24-42 are pending in the application.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24-42 are unclear in the recitation of a "biological sample". The metes and bounds of a biological sample cannot be determined. It is not clear what would be considered a biological sample and what would not.

Claims 24-42 are unclear in the recitation of a "biological agent". The metes and bounds of a biological agent cannot be determined. It is not clear what would be considered a biological agent and what would not.

Claims 34-36 are unclear in the recitation "wherein an antibody is used in carrying out said method". It is not clear if "an antibody" refers to the same antibody recited in claim 25, or if "an antibody" recited in claim 34 refers to some other antibody in the instant method.

Claim 38 is unclear in the recitation "wherein a probe or ligand is used in carrying out said method". It is not clear if "a probe or ligand" refers to the same probe or ligand recited in

claim 25, or if "a probe or ligand" recited in claim 38 refers to some other probe or ligand in the instant method.

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an in vitro method of detection of LNCAP cells or prostate tissue using the antibodies E99, J415, J533, and J591, does not reasonably provide enablement for methods of detecting normal, benign hyperplastic and cancerous prostate epithelial cells including *in vivo* imaging studies, using any agent which binds the extracellular region of PSMA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The specification discloses 4 antibodies (E99, J415, J533, and J591) which were raised to the prostate cancer cell line LNcAP. The antibodies are shown to react strongly with prostate tissue and not normal tissue *in vitro*, and stain viable LNcAP cells. The J591 monoclonal antibody is shown to become internalized after binding viable LNcAP cells. Further, by immunoprecipitation, the antibodies are shown to bind identical bands as the PSMA specific antibody 7E11. Competition studies were performed between the new antibodies. Finally, the new antibodies were shown to bind to tumor vasculature in general in fixed tissue *in vitro* studies.

The specification fails to provide sufficient guidance and objective evidence to enable one skilled in the art to predictably detect normal, benign hyperplastic and cancerous prostate epithelial cells , including *in vivo* detection, using agents or antibodies that bind the extracellular domain of PSMA and target tumor vasculature. The PSMA antigen has been shown in the art to be specifically expressed in prostatic tissue. The instant demonstration that new antibodies E99, J415, J533, and J591 bind to vasculature in fixed tissue does not render it predictable that the new antibodies are binding to PSMA or that PSMA is expressed by vascular endothelial cells of tumors in general. The cell line used to raise the instant antibodies expresses tumor specific antigens which may not necessarily be prostate specific. While the new antibodies E99, J415, J533, and J591 recognize the same size band by immunoprecipitation as does 7E11, there is no direct objective evidence supplied that the antibodies are binding the same antigen. Competition studies are performed between the new antibodies to show they are, in the case of E99, J533, and

J591, binding the same antigen, but the 7E11 antibody fails to block any of the new antibodies in competition studies, indicating that the antibodies at least bind different epitopes. This provides no evidence to confirm binding of the same antigen. While the antigen recognized by the antibodies E99, J415, J533, and J591 appears to be expressed in normal prostatic tissue, on LNcAP cells, and in tumor vasculature, there is insufficient objective evidence to render it predictable that the antigen is PSMA. Likewise monoclonal antibody J591 is shown to be internalized after binding to LNcAP cells, however since it is not predictable that the antigen bound is the extracellular domain of PSMA, it is also unpredictable and would require undue experimentation to bind agents to PSMA which are also internalized.

In addition, the specification provides evidence of the ability of the antibodies to target tissues *in vitro* for detection but provides insufficient objective evidence that antibodies to the PSMA extracellular domain, or the antibodies E99, J415, J533, and J591 effectively target tumor vasculature in vivo. Jain, R.K. et al., Cancer and Metastasis Reviews (IDS) teaches that the efficacy in cancer therapy of novel therapeutic agents such as monoclonal antibodies, cytokines, and effector cells has been limited by their inability to reach their target *in vivo* in adequate qualities. Three physiological factors responsible for poor localization of macro molecules in tumors have been identified: (I) heterogenous blood supply, (II) elevated interstitial pressure which lowers fluid extravasation, and (III) large transport distances in the interstitium. Furthermore, the average vascular surface area decreases with tumor growth, hence reducing transvascular exchange in large tumors compared to smaller tumors. The molecule may also

bind non-specifically to proteins or other tissue components, bind specifically to the target and/or be metabolized which further lowers the effective diffusion rate by reducing the amount of mobile molecule. Finally, although the effector cells are capable of active migration, peculiarities of tumor vasculature and interstitium may also be responsible for poor delivery. In addition to the factors discussed previously, antigenic variables, such as intensity of antigen expression, heterogeneity of antigen expression, the chemical nature, location, and accessibility of the target antigen, as wells as antibody variables such as clearance mechanisms and persistence in tissues affect the outcome of *in vivo* based antibody methods.

Furthermore, applicant has provided no evidence that the new antibodies bind to prostate tissue *in vivo*. As set forth above, *in vivo* antibody methods are unpredictable and generally lack correlation to *in vitro* results due to physiological, antigenic, and other factors. Further, it is not clear that the new antibodies bind to a prostate specific antigen. Therefore, absent evidence, it is not clear that the new antibodies would bind to any prostate material *in vivo*, and even if they did bind *in vivo*, it is not clear what they would bind to, or if said binding would be useful for prostate tissue detection.

Therefor one of ordinary skill in the art would not have been enabled to practice the full scope of the invention as claimed.

Claim Rejections - 35 USC § 102

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who

has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 24-34, and 38-42 are rejected under 35 U.S.C. 102(e) as being unpatentable over Israeli et al., US Patent 5,538,866, of the IDS.

Israeli et al. teaches a method of detecting normal, benign hyperplastic, or prostate tissue, including in vivo, in urine or serum, or tissue samples, comprising providing a biological agent, (monoclonal or polyclonal)antibody, or ligand which when contacted with an extracellular domain of prostate specific membrane antigen present as an integral membrane protein of a living cell binds to the extracellular domain of prostate specific membrane antigen, wherein the biological agent is bound to a label, including short range radiation emitters, effective to permit detection of prostate specific membrane antigen (PSMA), contacting the biological sample with a biological agent having a label under conditions effective to permit binding of the biological agent to the PSMA proximate to or within the sample and detecting the presence of cancerous tissue by detecting the label. Although Israeli does not explicitly state that the antibody or ligand binds to the extracellular domain of prostate specific membrane antigen present as an integral membrane protein of a living cell, Israeli teaches in general antibodies which bind PSMA, and includes extensive structural information including the entire nucleic acid sequence of the antigen and the guidancer necessary to create antibodies to any portion of the antigen. Further, although Israeli et al. is silent as to the internalization of bound antibody, the redistribution and internalization of surface antigens and antibodies bound to them is a well known art phenomenon

(Coleman et al., page 76, column 2, 3rd paragraph) Israeli et al. further includes administration by various techniques and with a pharmaceutically and physiologically acceptable carrier (for example saline).(in Israeli, for example, see abstract, column 3, lines 1-22, column 6, lines 44-column7, line 43, column 11 - line 36-49, column 12 - line 32-65, and column 13 - line 10-21) Although Istaeli does not specifically recite rectal detection, or detection after prostatectomy, these are art standard methods of prostate cancer and cell detection and moitoring.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 24-34, and 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Israeli et al., US Patent 5,538,866, in view of Schlom, Molecular Foundations of Oncology, both of the IDS.

Israeli et al. teaches as applied to claims 24-34, and 38-42 supra. Israeli et al. fails to teach the specific art known engineered antibody variants recited in claim 37.

Schlom teaches engineered antibody modifications and labeling techniques which are now standard in the art, and which are useful for purposes of increase effectiveness and decreased antigenicity.(page 97, last paragraph)

Therefor it would have been prima face obvious to one of ordinary skill in the art at the time the invention was made to combine the art known engineered antibody variants of with the detection techniques of Israeli et al., and one would have been motivated to do so to increase effectiveness and decreased antigenicity.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Nichols, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Nichols, Nee Hunt

September 11, 2000

No claims are allowed.

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